of mature osteoclasts. The Examiner argues that there is no teaching of an antibody which affects these processes and therefore the claimed invention is not enabled. Applicant disagrees.

The burden for establishing a *prima facie* case of nonenablement has been set forth in *In re Wright* 27 USPQ2d 1513 (Fed. Cir. 1993.

> When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement.

The criteria for undue experimentation has been set forth in *In re Wands* 8 USPQ2d 1404 (Fed. Cir. 1984). *Wands* is also relevant in the present case since the subject matter alleged to lack enablement related to antibodies having a given affinity (or greater) for the antigen.

Applicant maintains that the Examiner has not met the burden for establishing a *prima facie* case of nonenablement because no reasonable explanation was provided as to why the disclosure is not enabling and no reasons were provided to doubt the teachings of the specification. Moreover, contrary to the Examiner's assertions, the findings in *Wands* are consistent with and support enablement of the claimed invention.

The Examiner has alluded to the quantity of experimentation necessary to identify anti-OPGbp antibodies which inhibit bone resorption. However, no explanation has been presented as to why the quantity of experimentation necessary to identify such antibodies would be undue and excessive. Moreover, this unsupported assertion is clearly contrary to *Wands*. The Court recognized that experimentation in the antibody field, such

as routine screening of hybridomas, is expected and practitioners of this art are prepared to undertake such screening to identify antibodies having the desired characteristics. 8 USPQ2d 1406, 1407. The present disclosure provides methods for screening anti-OPGbp antibodies for desired characteristics, such as inhibiting bone resorption. Example 8 describes an assay for determining increased osteoclastogenesis using OPGbp; Example 9 describes an assay for measuring increased bone resorption using OPGbp. One skilled in the art could readily add an anti-OPGbp antibody to one or both assays to determine the effects of an antibody on bone resorption. Moreover, the specification at p. 18, line 6, clearly contemplates adding antibodies to these assays:

> Antibodies can be tested for binding to the OPG binding protein in the presence and absence of OPG and examined for their ability to inhibit ligand (OPG binding protein) mediated osteoclastogenesis and/or bone resorption.

Screening of antibodies to identify those which inhibit bone resorption may be carried out without undue experimentation as it is fully described and enabled in the application.

The Examiner has repeatedly pointed out the lack of any actual examples of antibodies which inhibit bone resorption *in vitro* or *in vivo*. A lack of working examples does not, by itself, lead to a conclusion of nonenablement. This is particularly true when, as in the present case, other factors clearly point to and are consistent with enablement. In addition, it is well established that the enablement requirement under section 112 may be satisfied either through broad terminology or illustrative examples. *In re Marzochi* 169 USPQ 367, 369 (CCPA, 1971). In the present case, Applicant has provided the appropriate materials and methodology for obtaining anti-OPGbp antibodies in Example 11 of the specification.

Screening of those antibodies for the ability to inhibit osteoclast formation and bone resorption may be carried out as described in Examples 8 and 9, respectively. Applicant maintains that the disclosure provides illustrative examples which satisfy the enablement requirement. The Examiner has not pointed out why these examples are insufficient to enable the claimed invention.

The Examiner characterizes the art as unpredictable based on a general unsupported assertion that one skilled in the art could not predict how antibody binding to a ligand would affect the binding of that ligand to its receptor, and how antibody binding would affect the resulting activity of the ligand bound to a receptor. No document has been cited in support of this allegation. However, it was known in the art as of the priority date of the application that antibodies can neutralize or inhibit the activity of the antigens to which they bind. Applicant submits herewith as Exhibits A and B two such examples. Yamamato et al. (Microbiol. Immunol. 32, 339-350 (1988) provided as Exhibit A) describes three antibodies which neutralize the activity of γ-interferon. Two of the antibodies inhibit binding of γ-interferon to its receptor. Siegel et al. (Cytokine 7, 15-25 (1995) provided as Exhibit B) describes an antibody which neutralizes the activity of tumor necrosis factor (TNF)-α and blocks binding of TNF to TNF receptors. These references indicate that the art would not have discouraged one from obtaining inhibitory antibodies to a given target molecule.

The Takahashi reference has been cited by the Examiner in support the rejection. However, the reference supports enablement of the claimed invention. On p. 453 in the section entitled "Role of ODF/OPGL/TRANCE/RANKL in Osteoclast Function", the authors point out that ODF (or OPGbp) induces the activity of osteoclasts and that sODF (soluble ODF or soluble OPGbp) "induced resorptive activity of purified osteoclasts". The authors also state that an " … anti-ODF (anti-OPGbp) antibody completely

abolished the effects of these bone-resorbing factors". (p. 453, right hand column). The statement in the Takahashi reference that an anti-OPGbp antibody inhibits bone resorption clearly supports enablement of the invention.

The Examiner alleges without any support whatsoever that there is a lack of guidance in the specification. The following are examples of guidance in the specification for the claimed invention:

> … antibodies which bind to OPG binding protein and block interactions with other binding compounds may have therapeutic use in modulating osteoclast differentiation and bone resorption. (p. 17, line 35 to p. 18, line 3)
>
> Antibodies to the OPG binding protein may be useful in the treatment of bone diseases … . (p. 18, lines 4 and 5).
>
> Antibodies can be … examined for their ability to inhibit ligand (OPG binding protein) mediated osteoclastogenesis and/or bone resorption. (p. 18, lines 6-10).

The Examiner has not provided any reasons to doubt these statements and has not pointed out why these and other statements in the application do not provide an enabling disclosure.

The Examiner has alluded to the breadth of the claims as a factor is considering enablement, although there was no explanation as to why the claim scope was not enabled. In *In re Fisher* 166 USPQ 24 (CCPA, 1970), it was held that the scope of claims must bear a "reasonable correlation" to the scope of enablement provided by the specification. In the present case, the scope of the claims are commensurate with the scope of enablement as both the claims and the enabling disclosure relate to anti-OPGbp antibodies which inhibit bone resorption and the use thereof of said antibodies. As argued above, Applicant maintains that the disclosure enables the use of such antibodies.

In *Wands*, it was noted that those in the antibody field had a "high level of skill". 8 USPQ2d 1406. Accordingly, given that level of skill in the art, one would have been able to carry out the claimed invention without undue experimentation

Declaration of John K. Sullivan

In addition to the above remarks, Applicant provides herewith as Exhibit C a Declaration of John K. Sullivan describing anti-OPGbp antibodies which inhibit bone resorption.

The following experimental results are presented:

1) Paragraphs 6 and 7 describe the identification of polyclonal antibodies generated by immunizing rabbits with various OPGbp peptides and polypeptides, such as a BB' loop-Cys peptide, an EF loop6-Cys peptide and human OPGbp[159-317].

2) Paragraph 8 and Attachment No. 1 show binding of the anti-OPGbp antibodies to murine and human OPGbp by EIA.

3) Paragraph 9 and Attachment No. 2 show inhibition of osteoclastogenesis *in vitro* by anti-BB' and anti-human OPGbp[159-317] antibodies.

4) Paragraph 10 and Attachment No. 3 show inhibition of bone resorption and increased bone density *in vivo* by anti-human OPGbp[159-317].

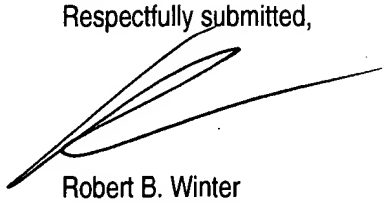
In view of these results, it is clear that antibodies for use in the claimed methods may be obtained without undue experimentation by one skilled in the art following the teachings of the specification.

Applicant respectfully requests withdrawal of the rejection.

CONCLUSION

In view of the remarks set forth above, Claims 37-49 are in condition for allowance and an early notice thereof is solicited.

Respectfully submitted,



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